UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Note to Reader
September 9, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply, EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, if unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues

available in the information in this docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack Housenger, Acting Director
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CYANAMID

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August 20, 1998

Mr. Calvin Furlow
Public Information and Records Integrity Branch
Information Resources and Services Division [7502C]
Office of Pesticide Programs, Rm# 119, CM-2
Environmental Protection Agency
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Re: Comment to Docket OPP-34139
Response to Preliminary Risk Assessment of Occupational Exposure to Terbufos

Dear Sir/Madam:

This letter and attachment are germane to the reregistration of terbufos and the Agency's preliminary risk assessment on occupational exposure therefore we respectfully request that this entire document be placed in the non-confidential section ("CBI code A") of the EPA's Office of Pesticide Programs' public docket for terbufos.

On August 12, 1998 EPA publicly released a preliminary risk assessment of occupational exposure to terbufos along with supportive internal EPA documents on the subject. An internal EPA memorandum found in the docket from J. Dawson to W. Hazel dated March 4, 1998 states that since:

> "no chemical-specific exposure data were submitted in support of the [assessment]...all exposure calculations were based on surrogate exposure calculated using the Pesticide Handlers Exposure Database (PHED)."

The memorandum continues with:

> "The PHED surrogate exposure data upon which this [preliminary] assessment was based is low quality data. The PHED exposure estimates...have been reevaluated, but even the revised values are still considered low quality data."

The Agency concludes:

> "The real refinement [to the preliminary occupational exposure assessment] will come from the development of chemical-specific exposure data and by addressing the dermal absorption/dermal toxicity issue."

In order to provide EPA with appropriate data to more truly assess potential worker exposure to terbufos, American Cyanamid Company conducted two worker exposure studies and two dermal toxicity studies with the formulated products: COUNTER® 15G systemic insecticide-nematicide and COUNTER® CR® systemic insecticide-nematicide (EPA Reg. Nos. 241-238 and 241-314, respectively).

Attachment 1 to this letter contains a summary of this work to date.

The studies will address the Agency's concern over the use of "low quality" surrogate exposure data (i.e., PHED) in the preliminary risk assessments by providing exposure data derived in the field by farm workers handling and applying the COUNTER products under typical use scenarios. The toxicology studies will address the dermal absorption/dermal toxicity issue by providing a more appropriate toxicological end-point based on the formulated products actually used in the field by farmers rather than an end-point based on orally-dosed technical terbufos as is currently used in the Agency's preliminary assessments.

Interim results from the dermal toxicity studies alone indicate that Margins of Exposure (MOE) should be at least 150-fold higher (i.e., 150-fold less risk) for the 15G formulation and 400-fold higher for the CR formulation than is currently presented in the Agency's preliminary risk assessments.

These toxicology data, in conjunction with results from the worker exposure studies, are expected to significantly refine the Agency's occupational exposure assessment and show that the use COUNTER products according to label directions does not pose an unacceptable risk to farm workers. Final reports of the work is expected by March 1999.

Lastly we would like to make you aware of an inappropriate calculation used in the Agency's preliminary worker exposure assessment pertaining to inhalation exposure to terbufos. This is also addressed in Attachment 1. By using the correct calculation to determine the dose corresponding to a No Observable Effect Level (NOEL) of 0.01 ug/L,

the inhalation MOEs are expected to increase by at least 2.4-fold above (i.e., 2.4-fold less risk) than is currently used by the Agency. Actual inhalation exposure (in comparison to the surrogate data derived from PHED) is being measured in the field in the worker exposure studies mentioned above.

Please contact me at telephone number 609-716-2378 should you have any questions.

Sincerely,

John J. Wrubel

John J. Wrubel
Product Registrations Manager
U.S. Plant Regulatory Affairs

cc: A. Chiri, OPP/SRRD
W. Hazel, OPP/HED
M. Mautz, OPP/RD

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ATTACHMENT I

TERBUFOS:
NEW DATA FOR WORKER EXPOSURE RISK ASSESSMENTS

Terbufos is an organophosphate insecticide and nematicide formulated as a granular product containing either 15% active ingredient (ai) on a clay-based granule (COUNTER® 15G) or 20% ai on a polymer-based granule (COUNTER® CR). Terbufos is currently registered for use on corn, grain sorghum and sugar beets and is applied to the soil as a band or in-furrow, both requiring soil incorporation. Corn treatments account for greater than 85% of the product's usage.

Preliminary worker exposure risk assessments have been performed by the U.S. EPA during the re-registration process for terbufos. In these assessments, the Agency used surrogate data from the Pesticide Handlers Exposure Database (PHED) to estimate potential dermal and inhalation exposure to workers. For dermal occupational risk assessments, the dermal exposure estimates were adjusted for systemic exposure by a 100% dermal absorption factor. The dermal exposure estimates (adjusted for systemic exposure) were then compared to the No-Observable Effect Level (NOEL) of 0.005 mg/kg b.w./day from the 28-day oral study in dogs. This NOEL was based on a biologically significant (approximately 36%), as well as a statistically significant (males only), reduction in plasma cholinesterase activity at 0.015 mg/kg b.w./day, the highest dose tested. The reduction in plasma cholinesterase activity was observed in the absence of clinical signs of cholinergic toxicity (NOEL > 0.015 mg/kg b.w./day), as well as in the absence of an effect on brain or red blood cell (RBC) acetylcholinesterase activity (NOEL > 0.015 mg/kg b.w./day). In fact, the one-year oral dog study with terbufos suggests that the NOEL for both brain and RBC acetylcholinesterase inhibition is 0.06 mg/kg b.w./day, while the NOEL for clinical signs of cholinergic toxicity (i.e., tremors) is 0.09 mg/kg b.w./day.

For inhalation occupational risk assessments, the Agency used the NOEL of 0.01 µg/L (analytical) from the 14-day repeat-dose whole-body inhalation study in rats with terbufos. This NOEL was incorrectly converted to a dose (on a mg/kg b.w. basis) using the breathing rate and body weight of a human rather than that from a rat. This dose was then compared to inhalation exposure estimates derived from PHED. The results from both the dermal and inhalation occupational exposure risk assessments showed unacceptable margins of exposure (i.e., < 100) for workers.

To more realistically evaluate the occupational dermal and inhalation risk to farm workers, American Cyanamid Company recently conducted two worker exposure studies. EPA reviewed and approved the protocols for these two studies. One study was conducted with COUNTER 15G in a LOCK 'n LOAD® closed handling system while the second study was conducted with COUNTER CR in bags. Both studies included loading and application of COUNTER to corn at the typical labeled use rate at 15 different sites. For both studies, dermal exposure to terbufos was evaluated by analyzing whole-body dosimeters worn by each loader and applicator, as well as face wipe and hand wash

samples. Inhalation exposure to terbufos was evaluated by analyzing air monitoring tubes worn by each loader and applicator. The field portions of both studies have been completed and samples are presently being assayed. Results from these two studies are expected to show that EPA levels of concern will not be exceeded when COUNTER products are loaded and applied under actual use conditions. It is expected that the final reports for these two studies will be completed by March of 1999.

In addition to conducting the two occupational exposure studies, two repeat-dose dermal toxicity studies have been conducted to provide more appropriate NOELs for inclusion in dermal occupational risk assessments. One repeat-dose (4-week) dermal toxicity study was conducted with COUNTER 15G, while the other repeat-dose (4-week) dermal study was conducted with COUNTER CR. Both studies included measurements of plasma cholinesterase and RBC acetylcholinesterase activities at several time points during the study, while brain ACHE activity was measured at study termination. In the study with COUNTER 15G, 5 groups of 10 Sprague-Dawley rats/sex received a dermal dose of the test material for 6 hours/day, 5 days/week, for 4 weeks at dose levels of 0, 2, 5, 10 or 25 mg/kg b.w./day. The NOEL from this study was 5 mg/kg b.w./day (0.75 mg ai/kg b.w./day) based on statistically significant decreases in plasma cholinesterase activity (30% and 67% inhibition) and red blood cell (RBC) and brain acetylcholinesterase activities (61% and 71% inhibition for RBCs, and 17% and 18% inhibition for brain) for males and females, respectively, at 10 mg/kg b.w./day, the next highest dose tested. Results from this dermal study conducted with COUNTER 15G were submitted to the U.S. EPA in March, 1998, and assigned an MRID Number of 44520501.

In the dermal study with COUNTER CR, 3 groups of 10 female Sprague-Dawley rats received a dermal dose of the test material for 6 hours/day, 5 days/week, for 4 weeks at dose levels of 0, 5, or 10 mg/kg b.w./day. (Male rats were not included in this study as female rats are more sensitive to terbufos than males.) Preliminary cholinesterase data from this study support a NOEL of 10 mg/kg b.w./day (2.0 mg ai/kg b.w./day). This study is intended for submission to the US EPA in October of 1998. Statistically significant reductions in plasma and RBC cholinesterase activities (up to 62% for plasma and up to 73% for RBCs) for males and females and a slight, non-statistically significant reduction in brain acetylcholinesterase activity for females (21%) at 25 mg/kg b.w./day were observed in a previous range-finding dermal toxicity study with COUNTER CR which was submitted to the US EPA in December of 1997.

A review of the acute toxicity database for both the COUNTER 15G and CR formulated products indicates less than 100% dermal absorption of terbufos from the formulated products [acute oral LD_{50} for technical terbufos (89.7% a.i.) is 3.2 mg/kg b.w. (males) and 1.5 mg/kg b.w. (females) as compared to dermal LD_{50} values of 123 mg/kg b.w. (males) (18.4 mg a.i./kg b.w.) and 71 mg/kg b.w. (females) (10.6 mg a.i./kg b.w.) for the 15 G formulation and 566 mg/kg b.w. (males) (113.2 mg a.i./kg b.w.) and 238 mg/kg b.w. (females) (47.6 mg a.i./kg b.w.) for the CR formulation]. These data suggest that the dermal absorption of terbufos from the 15G formulated product is approximately 15%, while the dermal absorption of terbufos from the CR formulated product is only

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approximately 3%, rather than 100% as assumed by the EPA. A higher NOEL for the dermal toxicity study with COUNTER CR (10 mg/kg b.w./day) compared to the NOEL for the dermal toxicity study with COUNTER 15G (5 mg/kg b.w./day) is consistent with the lower predicted dermal absorption value of terbufos from the CR formulated product compared to that from the 15G formulated product, even though the CR formulated product contains approximately 20% ai versus 15% ai for the 15G formulated product.

It is the considered opinion of American Cyanamid Company that results from the repeat-dose dermal toxicity studies with COUNTER 15G and COUNTER CR should be utilized by the EPA to define NOELs and subsequent dermal MOEs for workers, rather than data from the 28-day oral dog study. Firstly, in the repeat-dose dermal toxicity studies, animals were exposed to formulated terbufos rather than technical material. Because the worker will not be exposed directly to the active ingredient, but rather to active ingredient contained within clay (15G) or polymer (20CR) granules, these studies more closely simulate potential exposure of the worker. Secondly, animal toxicity data following dermal exposure to the terbufos end-use formulations are more suitable for extrapolation of worker risk via the dermal route, and thus, will eliminate the use of data from a study with a less appropriate route of exposure. Finally, if a NOEL from an oral toxicity study is used in dermal risk assessments, the estimated systemic exposure of dermally exposed workers assumes 100% dermal absorption. However, as noted above, a 100% dermal absorption value for terbufos formulated as either 15G or CR granules is overly conservative, especially given that both the clay and polymer-based granules are designed to promote the safe use of these products.

Once the exposure data become available from the two farm worker exposure studies, more realistic exposure assessments can be made for workers loading/applying COUNTER 15G and COUNTER CR. Dermal exposure values obtained from the worker exposure study with COUNTER 15G should be compared to the NOEL of 5 mg/kg b.w./day (0.75 mg ai/kg b.w./day) from the dermal toxicity study with COUNTER 15G, while dermal exposure values obtained from the worker exposure study with COUNTER CR should be compared to the NOEL of 10 mg/kg b.w./day (2.0 mg ai/kg b.w./day) from the dermal toxicity with COUNTER CR. The dermal NOELs of 5 and 10 mg/kg b.w./day (0.75 mg ai/kg b.w./day for COUNTER 15G and 2.0 mg ai/kg b.w./day for COUNTER CR) are 150-fold and 400-fold higher, respectively, than the orally-derived NOEL of 0.005 used by EPA in their preliminary evaluations. As such, dermal margins of exposure for workers should also increase by at least 150- to 400-fold compared to those originally calculated by the Agency.

Inhalation exposure values derived from the worker exposure studies should be compared to the NOEL from the 14-day repeat-dose inhalation toxicity study with terbufos technical. In this study, 5 groups of 10 Sprague-Dawley rats/sex were exposed to terbufos technical via whole-body inhalation exposure, for 8 hours/day, 5 days/week for 2 weeks at concentrations of 0, 0.01, 0.02, 0.05, or 0.1 µg/L (analytical). The study report indicates that the NOEL for this study is 0.02 µg/L, based on statistically significant reductions in plasma and RBC cholinesterase activities for males and females at 0.05 µg/L,

the next highest concentration tested. However, the Agency cited the lowest concentration of 0.01 µg/L as the NOEL for this study, based on an apparent high level of variability in chamber concentrations of terbufos.

Before data from this 14-day inhalation toxicity study can be used in inhalation risk assessments for workers, the NOEL must be converted to a corresponding dose on a mg/kg b.w. basis. In their draft Health Effects Division (HED) science chapter (1995), the Agency converted the NOEL of 0.01 µg/L (0.01 mg/m^3) to a dose of 0.0014 mg/kg b.w./day for inclusion in inhalation risk assessments for workers. However, the Agency used the breathing rate for a human (10 m^3 for an 8-hour work day) and body weight for a human (70 kg), rather than those for a rat to convert this NOEL of 0.01 µg/L to a corresponding dose of 0.0014 mg/kg b.w./day (0.01 mg/m^3 x $10m^3$/day ÷ 70 kg = 0.0014 mg/kg b.w./day). Because rats, and not humans, were tested in the 14-day inhalation study with terbufos, the concentration of 0.01 µg/L must be adjusted by the breathing rate of the rat (10.5 L/hour)[1] and the average body weight of the rats in the study (0.245 kg for female rats, the more sensitive of the two sexes to terbufos). Adjusting the concentration of 0.01 µg/L for the breathing rate and body weight of the rat, as well as for the exposure time, results in a corresponding dose of 0.0034 mg/kg b.w./day (see below):

0.01 µg/L x 10.5 L/hr x 8 hr/day ÷ 0.245 kg = 3.43 µg/kg =
0.00343 mg/kg b.w./day.

A dose of 0.0034 mg/kg b.w./day (corresponding to a NOEL of 0.01 µg/L) is 2.4-fold higher than a dose of 0.0014 mg/kg b.w./day, as calculated by the U.S. EPA. As such, inhalation margins of exposure for workers should also increase by at least 2.4-fold compared to those originally calculated by the Agency.

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[1] John E. Whalan and Hugh M. Pedttigrew. Inhalation Risk Assessments and the Combining of Margins of Exposure. Health Effects Division, Office of Pesticide Products, U.S.EPA, February 10, 1997.